

In re Appln. of Dudley et al.
Attorney Docket No. 233876

CLAIM AMENDMENTS

1. (Original) A method of promoting the regression of a cancer in a mammal, which method comprises:

(i) administering to the mammal nonmyeloablative lymphodepleting chemotherapy, and

(ii) subsequently administering:

(a) autologous T-cells, which have been previously isolated, selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, and rapidly expanded *in vitro* only once, and, either concomitantly with the autologous T-cells or subsequently to the autologous T-cells, by the same route or a different route, a T-cell growth factor that promotes the growth and activation of the autologous T-cells, or

(b) autologous T-cells, which have been previously isolated, selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, modified to express a T-cell growth factor that promotes the growth and activation of the autologous T-cells, and rapidly expanded *in vitro* only once, whereupon the regression of the cancer in the mammal is promoted.

2. (Original) The method of claim 1, wherein the T-cell growth factor is interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-15 (IL-15), or a combination of two or all of the foregoing.

3. (Currently Amended) The method of claim 1 or 2, wherein the nonmyeloablative lymphodepleting chemotherapy comprises the administration of cyclophosphamide and fludarabine.

4. (Original) The method of claim 3, wherein around 60 mg/kg of cyclophosphamide are administered for two days after which around 25 mg/m² fludarabine are administered for five days.

5. (Original) The method of claim 4, wherein the cyclophosphamide and fludarabine are administered intravenously.

6. (Currently Amended) The method of claim 2 ~~any of claims 2-5~~, wherein a

dose of about 720,000 IU/kg of IL-2 is administered three times daily until tolerance.

7. (Original) The method of claim 6, wherein from about 5 to about 12 doses of IL-2 are administered.

8. (Original) The method of claim 7, wherein around 9 doses of IL-2 are administered.

9. (Currently Amended) The method of claim 6 ~~any of claims 6-8~~, wherein the dose of IL-2 is administered as a bolus intravenous injection.

10. (Currently Amended) The method of claim 1 ~~any of claims 1-9~~, wherein from about 2.3×10^{10} T-cells to about 13.7×10^{10} T-cells are administered.

11. (Original) The method of claim 10, wherein around 7.8×10^{10} T-cells are administered.

12. (Currently Amended) The method of claim 1 ~~any of claims 1-11~~, wherein the T-cells are administered as an intravenous infusion.

13. (Original) The method of claim 12, wherein the intravenous infusion lasts approximately 30-60 min.

14. (Currently Amended) The method of claim 1 ~~any of claims 1-13~~, wherein the cancer is melanoma.

15. (Original) The method of claim 14, wherein the T-cells bind to melanoma antigen recognized by T-cells-1 (MART-1).

16. (Currently Amended) The method of claim 1 ~~any of claims 1-15~~, wherein the cancer is metastatic.

17. (Currently Amended) The method of claim 1 ~~any of claims 1-16~~, wherein the mammal is a human.

18. (Original) A method of promoting the regression of metastatic melanoma in a human, which method comprises:

(i) intravenously administering around 60 mg/kg of cyclophosphamide for two days followed by around 25 mg/m^2 fludarabine for five days, and

(ii) subsequently intravenously administering:

(a) an infusion of around $2.3 \times 10^{10} - 13.7 \times 10^{10}$ autologous T-cells, which have been previously isolated, selected for highly avid recognition of MART-1, and rapidly expanded *in vitro* only once, and, either concomitantly with the autologous T-cells or subsequently to the autologous T-cells, a bolus of about 720,000 IU/kg of IL-2 three times daily until tolerance, or

(b) an infusion of around $2.3 \times 10^{10} - 13.7 \times 10^{10}$ autologous T-cells, which have been previously isolated, selected for highly avid recognition of MART-1, modified to express IL-2, and rapidly expanded *in vitro* only once, whereupon the regression of the metastatic melanoma in the human is promoted.

19. (Original) The method of claim 18, wherein around 7.8×10^{10} T-cells are administered.

20. (Currently Amended) The method of claim 18 or 19, wherein from about 5 to about 12 doses of IL-2 are administered.

21. (Original) The method of claim 20, wherein around 9 doses of IL-2 are administered.

22. (Currently Amended) The method of claim 18 ~~any of claims 18-21~~, wherein the intravenous infusion lasts approximately 30-60 min.

23. (Original) A method of promoting the regression of a cancer in a mammal, which method comprises:

(i) administering to the mammal nonmyeloablative lymphodepleting chemotherapy, and

(ii) subsequently administering:

(a) autologous T-cells, which have been previously isolated, selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, and, optionally, rapidly

expanded *in vitro* at least once by further stimulation with the antigen of the cancer, and, either concomitantly with the autologous T-cells or subsequently to the autologous T-cells, by the same route or a different route, a T-cell growth factor that promotes the growth and activation of the autologous T-cells, or

(b) autologous T-cells, which have been previously isolated, selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, modified to express a T-cell growth factor that promotes the growth and activation of the autologous T-cells, and, optionally, rapidly expanded *in vitro* at least once by further stimulation with the antigen of the cancer, whereupon the regression of the cancer in the mammal is promoted.

24. (Original) The method of claim 23, wherein the T-cell growth factor is IL-2, IL-7, IL-15, or a combination of two or all of the foregoing.

25. (Currently Amended) The method of claim 23 or 24, wherein the nonmyeloablative lymphodepleting chemotherapy comprises the administration of cyclophosphamide and fludarabine.

26. (Original) The method of claim 25, wherein around 60 mg/kg of cyclophosphamide are administered for two days after which around 25 mg/m² fludarabine are administered for five days.

27. (Original) The method of claim 26, wherein the cyclophosphamide and fludarabine are administered intravenously.

28. (Currently Amended) The method of ~~claim 24 any of claims 24-27~~, wherein a dose of about 720,000 IU/kg of IL-2 is administered three times daily until tolerance.

29. (Original) The method of claim 28, wherein from about 5 to about 12 doses of IL-2 are administered.

30. (Original) The method of claim 29, wherein around 9 doses of IL-2 are administered.

31. (Currently Amended) The method of claim 28 ~~any of claims 28-30~~, wherein the dose of IL-2 is administered as a bolus intravenous injection.

32. (Currently Amended) The method of claim 23 ~~any of claims 23-31~~, wherein from about 1.2×10^{10} T-cells to about 4.3×10^{10} T-cells are administered.

33. (Currently Amended) The method of claim 23 ~~any of claims 23-32~~, wherein the T-cells are administered as an intravenous infusion.

34. (Original) The method of claim 33, wherein the intravenous infusion lasts approximately 30-60 min.

35. (Currently Amended) The method of claim 23 ~~any of claims 23-34~~, wherein the cancer is melanoma.

36. (Original) The method of claim 35, wherein the T-cells bind to MART-1.

37. (Currently Amended) The method of claim 23 ~~any of claims 23-36~~, wherein the cancer is metastatic.

38. (Currently Amended) The method of claim 23 ~~any of claims 23-37~~, wherein the mammal is a human.

39. (Currently Amended) The method of claim 23 ~~any of claims 23-38~~, wherein the antigen of the cancer consists of amino acids 26-35 of MART-1, in which amino acid 27 has been replaced with leucine.

40. (Currently Amended) The method of claim 23 ~~any of claims 23-39~~, wherein the antigen of the cancer consists of amino acids 209-217 of gp100, in which amino acid 210 has been replaced with methionine.